REMARKS

Claims

Claims 7-14 are under examination with claims 1-6 previously cancelled without prejudice or disclaimer.

Claim amendments

Amended claim 7 and 9 are supported by the disclosure contained in, for example, page 3, lines 11–14 and Example D (paragraph bridging pages 9 and 10) of the originally-filed specification.

Amended claim 8 is drawn to the elected species. Entry thereof is respectfully requested.

Support for amended claims 13–14 can be found in, for example, at least the disclosure contained in the Examples.

It is respectfully submitted that the claim amendments do not raise new matter.

Claim objections

Applicants respectfully disagree with the PTO's contention that the recitation of acronyms HPLC and ACE in the claims constitutes informality. In view of Applicants' detailed disclosure and the skilled workers express knowledge of the terms, it is submitted that the terms are well-recognized in the art. However, in order to facilitate prosecution, claim 11 has been amended as per the Examiner's suggestion. The objection of claim 7 is moot in view of the amendments. Withdrawal of the objection is respectfully requested.

Restriction

At page 2 of the Office Action it is alleged that the claims in their current form are confusing because "Applicant has elected a single peptide (SEQ ID NO: 5) as the elected species (not traversed, and made FINAL at the last Office Action) out of two distinct fractions." Applicants respectfully disagree with this contention. At the outset, Applicants submit that the election of Group XIX (claims 3–6), drawn to a dietary supplement comprising the peptide of SEQ ID NO: 5, and SEQ ID NOs:8-10, was made with traverse. See, the response to the Restriction Requirement filed October 22, 2006. Based on the Examiner's willingness to examine the full scope of the claims, it is

assumed that there is no undue burden on the PTO and that the restriction requirement has been withdrawn.

In view of the claim amendments presented herein, Applicants respectfully submit that each of claims 7 and 9 sets forth a proper Markush group and that the claims should be examined in accordance with Markush practice. Under M.P.E.P. §803.02, should no prior art be found which renders the invention of the elected species unpatentable, the search of the remainder of the generic claim(s) should be continued in the same application.

Claim 7 is a proper Markush group and does not lack unity of invention. The same is true with claim 9. The Office Action appears to indicate that the peptide compounds recited in claim 9 are distinct from the compounds recited in claim 10. Applicants' specification teaches that the compounds in these claims clearly have unity of invention. In any event, the rules state that a Markush claim **can** contain independent and distinct inventions such that a prior art reference anticipating the claim with respect to one member would not render the claim obvious with respect to another member. The PTO's own rules on this matter set forth in M.P.E.P. §803.02 specifically state that:

> "A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other member(s)."

This section of the M.P.E.P. makes clear that such a claim is a proper Markush claim and should be examined in accordance with Markush practice. Applicants request that, should this rejection be maintained, authority be cited as to why this section of the M.P.E.P. is not applicable.

Applicants further submit that insofar as the compounds of the instant invention share *similar* structural features (for example, oligopeptide sequences) and functional activity (for example, ACE inhibition), a composition comprising the same duly satisfies the unity of invention requirement. Thus, Applicants' instant claims 7 and 9 meet the requirement for a proper Markush claim and the species recited therein should be examined on their merits. Favorable action is earnestly solicited.

Should the restriction requirement still be maintained, Applicants reserve the right to petition the restriction requirement in accordance with 37 CFR §1.144.

Rejections under 35 U.S.C. §102(b)

The rejections under 35 U.S.C. §102(b) as allegedly anticipated by Matoba et al. (*Agricultural and Biological Chemistry*, 34, 1235–1243), Zucht et al. (*FEBS Letters*, 372, 185–188, 1995), Brignon et al. (*FEBS Letters*, 76, 274-279, 1977) and Garault et al. (*JBC*, 277, 32-39, 2002) are respectfully traversed.

Matoba disclose bitter peptides (BP-I, BP-II, and BP-III) that are retrieved via sephadex G-25 column chromatography coupled to ion-exchange/paper chromatography of peptide products retrieved after hydrolysis of casein. See, sub-sections (d), (e), and (f) of the RESULTS sections of the cited reference. Manitoba does not teach a composition recited in Applicants' claims, for example, a composition comprising at least two peptides which are SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and/or SEQ ID NO: 5. The cited reference is silent as to the identity of the peptides in the eluted mixture other than SEQ ID NO: 5. Since not all aspects of the instant claims are taught or recited in Matoba, the cited reference cannot anticipate, keeping in mind that the PTO has the burden to demonstrate that the cited reference teaches the claimed composition. Withdrawal of the rejection is respectfully requested.

The rejection based on Zucht et al. is traversed inasmuch as the casocidin-I peptide recited in Figure 2 at page 187 of the cited reference is longer than the instantly claimed peptides. It is therefore courteously submitted that Zucht's casocidin-I polypeptide comprising 39 amino acid residues is *structurally distinct* from the constituents of the composition claimed herein. As such, the rejection must be withdrawn.

Brignon teaches the complete primary structure (i.e., polypeptide sequence) of α_{s2} casein. Brignon's polypeptide is longer and thus structurally distinct from the claimed polypeptides. Brignon generically mentions that a tryptic digest results in several fragmented peptides (labeled T1, T2, etc); however, Brignon is silent with respect to the structure of such tryptically cleaved products. There is no mention of a composition comprising the specific peptide sequence(s) recited in Applicants' claims. Moreover, the cited reference is silent with respect to a pharmaceutical composition recited in the claims and the activity thereof, for example, against ACE. Since not all

aspects of the instant claims are taught or recited in Brignon, the cited reference cannot anticipate. As such, the pending rejection over Brignon et al. must also be withdrawn.

Garault is drawn to transport of milk-derived oligopeptide activity in *S. thermopilus* bacteria. See, the INTRODUCTION section of the cited reference. There is no mention of a composition thereof as recited in the claims. For example, the cited reference fails to teach a peptide fraction comprising the polypeptide of SEQ ID NOs: 1-5, the structure of which is presented in the sequence listing page. Garault therefore fails to anticipate the instantly claimed subject matter. As such, the rejection must be withdrawn.

In summary, none of the aforementioned references teach a composition recited in Applicants' claims and further fail to disclose the activity of such compositions in a manner recited in Applicants' claims. As such, the references fail to anticipate or render obvious what is claimed herein. All the rejections must therefore be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

The contention that claims 7, 8, 11, 13, and 14 are non-enabled is respectfully traversed.

The Examiner finds the specification is enabling only for the food products but not for the pharmaceutical uses recited in the claims. The entirety of the PTO's arguments concerning non-enablement is centered upon the contention that "SEQ ID NO:5 has not been established as capable of treating hypertension or one of its underlying pathways." Insofar as the Office Action fails to provide any evidence on lack of enablement of the disclosed peptide species, these allegations have no legal basis.

At the outset, Applicants submit that the instant claims are drawn to a pharmaceutical composition comprising the claimed peptide(s). The recitation of the claim term "pharmaceutical" is not to be construed as limiting to the use thereof for example, in the treatment of diseases. For example, diagnostic uses are possible. In the absence of evidence which demonstrate otherwise, all claims must be taken to satisfy the requirements of 35 U.S.C. §112, ¶1. Moreover, only one use needs to be enabled for compound/composition claims. Here, the focus is on a composition which is capable of inhibiting ACE and is useful for the treatment of hypertensive diseases.

Applicants maintain all pending claims clearly satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. The Office Action mailed December 12, 2006 relies

on the *Wands* factors and allegations that the claims are very broad with respect to the use of the pharmaceutical composition, for example, in the treatment of diseases. Applicants respectfully disagree with this allegation.

The instant specification describes a role of ACE in the etiology of hypertensive disorders. For example, see, the paragraphs bridging page 1 and 2 of the instant specification, as originally filed. It is described therein that ACE has a key role in vivo in regulating arterial pressure and that ACE inhibitors (captoproil, benazepril, enalapril, lisinopril, etc) are one of the main classes of molecules used for combating hypertension. Mechanisms via which ACE regulates atrial pressure, for example, via the rennin-angiotensin system, was recognized in the field well before the filing date of the instant application. This is clear from the referenced scientific publications by Weber et al. and Piepho et al., the abstracts of which are enclosed herewith. The Examiner is cordially requested to review the scientific disclosure contained in these references.

It is respectfully submitted that the mere presentation of a rationale for the use of ACE inhibitors having the claimed pharmacological activity (for example, IC_{50} of 60μM or less) and information pertaining to the methods for using such, coupled with a disclosure of the molecules having such activity is sufficient for enablement. The rationale for the claimed end uses is clearly presented in Applicants' specification. See, for example page 2, lines 6–15.

The activity of the claimed composition against ACE is also clearly described. Using various biochemical and cellular assays, the specification provides an enabling disclosure of the *in vitro* activity of claimed peptide molecules. See, the paragraph bridging pages 9 and 10 of the specification, wherein it is expressly stated that "peak No. 4 containing the peptides FPQYLQY (SEQ ID No. 4) and FALPQYLK (SEQ ID No. 5), peak No. 3 containing the peptide FALPQY (SEQ ID No. 3), and peak No. 1 containing the peptide TVY (SEQ ID No. 1) inhibit ACE at more than 70%." A skilled artisan, in view of the detailed disclosure contained in the specification and the art knowledge of pharmacology would readily appreciate that the claimed molecules and/or compositions can be used in a manner described in Applicants' claims. Nothing more than routine experimentation would be required.

In summary, the specification provides enabling disclosures pertaining to the use of the claimed compositions in the modulation of ACE activity. Applicants' specification also provides an enabling disclosure for the use of such composition in therapeutics.

For example, the enclosed articles by Pan et al. and Li et al. disclose the anti-hypertensive effects of food-derived peptides. The publications clearly establish that the physiological effects of these peptides correlate with the inhibition of the target enzyme, ACE-I. See, for example, Fig. 2 and Fig. 4 of Pan et al. This is consistent with Applicants' claims. Furthermore, Li establishes the structural and functional correlation between small molecule ACE inhibitors (such as, for example, captoproil, benazepril, enalapril) and food-derived peptide compounds. See, the paragraphs bridging pages 475-477 of Li et al. Thus, Applicants' own specification, coupled with the knowledge on the structure/activity of both peptide and small-molecule ACE inhibitors, firmly supports enablement of ACE-inhibiting peptide compounds/compositions of the instant invention.

Given the extent of the disclosure provided, it would have at most involved routine experimentation, if any at all, for one skilled in the art to use the claimed molecules as pharmaceutical compositions. For example, see, page 3, lines 11–14. Formulations which confer targeted delivery or desired efficacy are routinely known in the art. Even absent the disclosure as discussed above, the rejection is clearly deficient under general controlling case law. The courts have placed a burden on the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated. See example *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). In contrast with the exhaustive disclosure, the present Office Action has not presented any evidence to refute the findings described in Applicants' specification; nor has the Office Action established any scientific credibility to support the contention that the claimed compositions could not be prepared and/or used in a manner described herein. Therefore, the rejection under 35 U.S.C. §112 is completely unfounded.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compositions recited in the claims. Instead of providing evidence of non-enablement, the Examiner cites the lack of predictability in the field of the hypertension, requiring additional working examples. However, based on the contentions raised in pages 7-8 of the prior Office Action, it appears that the PTO is requiring that the applicant meet the clinical standards as set forth by the FDA to satisfy that enablement requirement under 35 U.S.C. §112, ¶1. This is clearly not the intention of the statute. See, *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969). A lack of predictability can be addressed by routine experimentation which is permissible under the statute. A considerable amount of experimentation is

permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to direction which the experimentation should proceed (see *In re Wands* cited by the Examiner). Moreover, as stated in *In re Brana*, 51 F.3d 1516, 34 USPQ 1436 (Fed. Cir. 1995), an Applicant is not required to test the claimed compounds in their final use. The same rationale applies to meeting the enablement and disclosure requirements of 35 U.S.C. §112, first paragraph. The specification provides more than it needs, for example, *in vitro* assays and *in vivo* assays. In similar fashion, one of ordinary skill in the art by performing the same or similar tests can by routine experimentation determine the activity levels of each of the claimed compounds in treating hypertension.

For the reasons discussed above, applicants submit all pending claims satisfy the requirements of 35 U.S.C. §112, first paragraph. Withdrawal of the rejection is respectfully requested.

In view of the above-mentioned arguments and amendments, it is respectfully submitted that the claims in the application are in condition for allowance. However, if the Examiner has any questions or comments, he is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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Encl:

(a) Abstracts by:

- Weber et al., Am J Hypertens. 1999 Dec;12(12 Pt 3):189S-194S
- Piepho et al., Am J Health Syst Pharm. 2000 Oct 1;57 Suppl 1:S3-7.

(b) Articles by:

- Pan et al. (Food Chemistry, 2004)
- Li et al. (*Nutrition Research*, 2004)